Letter to the Editor on: “Population Pharmacokinetics of Dalbavancin and Dosing Considerations for Optimal Treatment of Adult Patients with Staphylococcal Osteoarticular Infections”. (Cojutti et al; doi: 10.1128/AAC.02260-20)

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Key words

Osteoarticular infections, dalbavancin, total concentrations, drug dosing adjustment
Dear Editor,

Recently, Cojutti et al. [1] published a population pharmacokinetic (POP PK) model on dalbavancin administered to adult patients with Staphylococcal osteoarticular infections (OAI). Based on this POP PK model, the authors proposed a drug dosage adjustment, i.e. a regimen of two 1,500 mg doses at a 1-week interval to ensure efficacy against both MSSA and MRSA for up to 5 weeks.

This information is particularly important as dalbavancin is being used more and more in France in patients with OAI, while the official indication is for acute skin and soft tissue bacterial infections in adults. However, clinicians who prescribe this off-label use of the drug are seeking information on dalbavancin exposure (plasma concentrations) for their patients. At Toulouse University Hospital, we conducted a retrospective cohort study approved by the Toulouse University Hospital review board (registration number: RnIPH 2021-78; CNIL number: 2206723 v 0). We documented plasma concentrations of dalbavancin for 33 patients with OAI. Their socio-demographic and biological characteristics are summarized in Table 1.

Using Cojutti’s POP PK model, we performed 10,000 Monte Carlo simulations for a perfusion (30 min) of 1,500 mg of dalbavancin. We plotted (Figure 1) the patients’ plasma concentrations (n=64; 1 - 7 samples/patient) measured by validated chromatography mass spectrometry. The comparison between the simulated and the measured concentrations showed that 42% of the measured concentrations (33% patients) were outside the 5th-95th percentile range, with 36% > the 95th and 6% < the 5th percentile. Therefore, this POP PK model tends to underestimate the concentrations observed in the French patients. Unfortunately, we have no reasonable explanation for this underestimation as (i) our patients had comparable socio-demographic characteristics, except for weight, however, overweight leads to
lower concentrations [2]; (ii) 90% of the French patients had a GFR ≥ 50 ml/min, suggesting no uncontrolled accumulation and (iii) 45% of the French patients presented severe (≤ 25 g/l) and 51% moderate hypoalbuminemia (>25 and ≤35 g/l). This last point is particularly important because in the absence of hypoalbuminemia, as was the case for the Italian population on which the POP PK model was based and validated [1], the French hypoalbuminemic patients should have had even higher measured concentrations. In fact, hypoalbuminemia is well-known to induce a decrease in protein-bound concentration and therefore in total concentration (measured concentration) for highly bound drugs such as dalbavancin (93%) [3], while unbound concentration (the active pharmacological form of the drug) is unchanged [4] [5] [6]. Consequently, for highly bound drugs, it is essential to assess the unbound concentration since measuring total concentration can lead to a misinterpretation of actual exposure.

The external evaluation of a POP PK model is not systematically performed, even if it is a requisite step [7]. Indeed, if external validation fails for a subpopulation, it is better to discard the model to avoid erroneous predictions and consequently erroneous drug dosage regimens for this subpopulation. In our case, considering that the PK profile of our patients was inaccurately described by Cojutti & al. [1], it is legitimate to question the relevance of the proposed dosage regimen for our French patients.

In conclusion, dosage regimens published in the literature should be used with caution when no external validation has been performed, especially when (i) they are based on a POP PK model built with a small cohort of patients without any significant covariate and (ii) they concern a drug highly bound to plasma proteins while only the total concentration is assessed.
Funding

This study was supported by internal funding.

Transparency declarations

None to declare

Acknowledgements

None to declare

References


Table 1: Socio-demographic and biological characteristics of patients from Cojutti’s publication [1] and 33 French patients

<table>
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GFR: glomerular filtration rate

Figure 1: Dalbavancin plasma kinetic profiles (n=10,000) simulated with the population pharmacokinetic model published by Cojutti et al. [1] for 1,500 mg perfused for 30 minutes. The median kinetic profile is indicated by the white curve. The "extreme" profiles found in less than 5% and 95% of the population are indicated by the black curves. The black squares represent observed trough concentrations for 33 patients with osteoarticular infection treated with 1,500 mg perfused over 30 minutes.
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